

MAP-kinases. As evidenced by ERK phosphorylation, concentrations as low as 0.1 ng/ml were sufficient for this mechanism. Pretreatment with pertussis toxin (PTX) inhibited MCP-1-dependent ERK phosphorylation. MCP-1 also induced secretion of matrix metalloproteinase (MMP)-2 which along with ERK activation was inhibited by PD98059.

Conclusion: The results demonstrate that MCP-1 can lead to direct activation of MAP kinases together with induction of MMPs in EC. Our data thus propose a new mechanism for the proatherogenic effect of MCP-1.

3:00 p.m.

860-5

Production of MCP-1 by Human Aortic Endothelial Cells, Upon Depletion of Nutrients, Requires Rac 1

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Background: Following an episode of coronary occlusion, inflammatory cells accumulate within small vessels of the coronary tree, and contribute to the injury that damages the myocardium. The chemokine monocyte chemoattractant protein-1 (MCP-1) is a key regulator of leukocyte recruitment to sites of inflammation. However, the exact molecular mechanism involved in controlling expression of MCP-1 in ischemic conditions remains unclear. The small GTP-binding protein Rac1 regulates the production of reactive oxygen species (ROS) by ubiquitous NADPH oxidase complex, the major source of superoxide in most cells. We investigated the effect of nutrient depletion, a condition associated with ischemia, on MCP-1 production in human aortic endothelial cells (HAEC) and the role of Rac-1 and reactive oxygen species in this process. **Methods:** Recombinant adenoviruses, for expression of either dominant negative (Rac1-N17) or constitutively active (Rac1-V12) mutants of Rac1, geranylgeranyltransferase inhibitor GGTI-298 (10uM), or N-acetylcysteine (20mM) were used to study the role of Rac1 and ROS in MCP-1 expression. Nutrient depletion (ND) was obtained by shifting HAEC from 10% to 0.5% FBS. MCP-1 production was measured by ELISA. **Results:** Nutrient depletion increased MCP-1 production by HAEC (4.8±0.66 fold, p<0.01), in a time dependent manner peaking at 24 hours. Expression of Rac1-V12 increased MCP-1 expression to a similar level, even in the absence of NP. Transduction of HAEC with Rac1-N17 at 25 MOI decreased NP-induced MCP-1 production (p<0.007). Likewise, NAC and GGTI-298, both decreased MCP-1 production (p<0.05 and p<0.001, respectively). **Conclusion:** These results suggest that nutrient depletion associated with ischemia is sufficient to induce MCP-1 production by HAEC, and that such production requires a functional Rac1, redox-sensitive, pathway.

3:15 p.m.

860-6

Motexafin Lutetium Phototherapy Induces Apoptosis in Macrophages and Downregulates Monocyte Chemoattractant Protein Expression in Human Coronary Artery Smooth Muscle Cells

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Background: Macrophage burden has been shown to be a main predictor for restenosis after percutaneous interventions. Monocyte chemoattractant protein (MCP-1) is a chemokine that is produced by stimulated endothelial cells and smooth muscle cells (SMCs), and is responsible for recruiting monocytes/macrophages into injured arterial walls. Motexafin lutetium (MLu), a photosensitizer, has been shown to reduce macrophage burden in experimental models. The mechanism by which MLu phototherapy reduces macrophages and the impact that phototherapy has on MCP-1 production was evaluated. **Methods:** The subcellular localization of MLu was evaluated in human THP-1 macrophages (ATCC) and coronary artery SMCs (Clonetics). Co-labeling studies were performed using organelle specific fluorogenic probes. After phototherapy, changes in nuclear morphology were assessed with Hoechst 33342 staining; lysosomal integrity was evaluated using fluorescence after acridine orange staining; cytochrome C and cathepsin B distribution were ascertained using immunofluorescence. Cellular viability experiments were performed with an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. RNA was harvested from SMCs for measurement of MCP-1 mRNA levels with the RiboQuant™ multi-probe RNase protection assay system (PharMingen). **Results:** MLu partitioned within macrophages and SMC lysosomes. Photosensitization led to lysosomal instability, release of intralysosomal cathepsin B into the cytoplasm, and the subsequent release of cytochrome C from the mitochondria. Chromatin condensation and nuclear blebbing, hallmark features of apoptosis, ensued. Photosensitization also caused downregulation of MCP-1 in human coronary artery SMCs. **Conclusions:** Considering the crucial and pivotal role that MCP-1 has in plaque progression, stabilization and in restenosis, it is likely that one of the mechanisms by which MLu-mediated phototherapy exerts its effect on plaque resolution is through the apoptotic elimination of macrophages and via the downregulation of MCP-1 production.

ORAL CONTRIBUTIONS

863 Vascular Disease Insights: Registry, Cohort, and Population Studies

Tuesday, March 19, 2002, 2:00 p.m.-3:30 p.m.
Georgia World Congress Center, Room 254W

2:00 p.m.

863-1

New Classification of Aortic Dissection With Improved Impact on Prognosis

Barbara M. Richartz, Dean E. Smith, Jeanna V. Cooper, Rajendra M. Mehta, Kim A. Eagle, Christoph A. Nienaber, on Behalf of International Registry of Acute Aortic Dissection (IRAD) Investigators, Ann Arbor, Michigan.

Background: The entry site location is currently used to classify and stratify acute aortic dissection. Type A lesions require urgent surgical therapy to improve survival, while type B lesions often have a better outcome and benefit from stenting or medical management. In the attempt to use anatomic information for assessment of prognosis we correlated the entry site location of type A and B aortic dissection with 30-day-mortality.

Methods: 820 patients with acute aortic dissection were enrolled in the database of the International Registry of Acute Aortic Dissection (IRAD). According to exact entry site location from diagnostic imaging we established 6 subgroups: aortic root (n = 197, 25%), ascending aorta (n = 291, 36%), arch (n = 69, 9%), left subclavian area (n = 157, 19%), descending thoracic aorta (n = 85, 10%), and abdominal aorta (n = 21, < 1%) and determined 30-day-mortality in each group.

Results: Among type A aortic dissections significant differences in 30-day-mortality were found with a death rate of 37% in aortic root, 28% in ascending aorta, and 23% in the arch [p < 0.001]. Conversely, in type B aortic dissection mortality did not differ between entry sites at left subclavian area (12%), descending thoracic aorta (13%), and abdominal aorta (10%). Demographic data were similar in all groups.

Conclusions: The closer the distance between entry site location and aortic root, the worse the prognosis of type A aortic dissection. Thus, prognosis in type A dissection is diverse and can be subclassified into 3 groups. Conversely, type B aortic dissection is homogeneous with respect to prognosis and subclassification is only descriptive.

2:15 p.m.

863-2

Familial Aortic Dissection/Aneurysm Associated With Patent Ductus Arteriosus: A New Entity?

Philippe Khau Van Kien, Alain Lalande, Caroline Bonnet, Arnaud Dellinger, Annie Petit, Anne Nivelon-Chevallier, François Brunotte, Xavier Jeunemaitre, Jean-Eric Wolf, CHU Bocage, Dijon, France.

Background: In March 2001, a first report from United States described an unusual family in which 5 members present a combination of thoracic aortic dissection/aneurysm (TAD/TAA) and patent ductus arteriosus (PDA). The authors suggested a possible common genetic defects. We report a large French family with the same association.

Subjects and methods: this family composed of 179 members was ascertained from a single probant. Forty first-degree relative subjects from three different generations have been enrolled in a clinical investigation protocol composed of two parts:

- a medical questionnaire concerning available medical records, state of health and allowing to investigate the familial history. A standardized clinical examination focused on classical signs of Marfan and Ehlers-Danlos syndromes.

- An annual long-term follow-up based on: standardized cardiovascular examination, transthoracic echocardiography and a thoracic MRI, completed by transesophageal ultrasonography when necessary, allowing the accurate measurement of the aorta, great vessels and heart. At the time of the inclusion, blood measurements of total and LDL-HDL cholesterol, triglycerides and glucose were performed.

Results: 9 cases of TAD and TAA among this family 4 TAD (2 males and 2 females) and 5 TAA (4 males and 1 female). All the cases of TAA have been discovered in asymptomatic subjects by screening. 8 cases of PDA without any particular neonatal context. 5 cases of cerebral stroke with two of them due to a documented intracranial carotidian aneurysm, 3 cases of suspicious sudden death. All these vascular findings cosegregate with cases of TAA/TAD in an autosomal dominant with incomplete penetrance pattern of inheritance. For all the probands there are no arguments for Marfan syndrome or Ehlers-Danlos syndrome vascular type. There is no particular familial context of arterial hypertension or atherosclerosis.

According to both families, aortic dissection/aneurysm with patent ductus arteriosus may be a new entity due to a common genetic defect that remains to be identified. Familial screening is very important in such a family that is still seldom recognized.

2:30 p.m.